UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,653	03/12/2001	Winfried Siffert	741135-12	6614

22204 7590 12/23/2003

NIXON PEABODY, LLP
401 9TH STREET, NW
SUITE 900
WASINGTON, DC 20004-2128

EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,653	SIFFERT, WINFRIED	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-17 and 28-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the reply filed September 25, 2003. Applicants arguments have been fully considered but are not persuasive to overcome the present grounds of rejection. This action is made final.

2. Acknowledgment is made of applicant's claim for foreign priority based on applications filed in Germany on 9/10/98, 2/25/98, 3/18/99, 3/29/99, 4/30/99, and 5/21/99. This claim to priority is set forth on the application data sheet. It is noted, however, that applicant has not filed a certified copy of these applications as required by 35 U.S.C. 119(b). Furthermore, Applicant is not entitled to priority to PCT/EP99/06534 because a certified copy of this document has not been provided. It is also noted, that this document is not in English and a certified translation would be required before priority can be evaluated.

In the response filed September 25, 2003, Applicants state that certified translations will be submitted under separate cover. However, these papers have not yet been received by the office.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) methods for determining whether an individual is more likely to show an increased reduction in coronary blood flow following treatment

with the -2 adrenergic agonist BHT 933 by assaying for the presence of the 825 T allele of the gene encoding the human G protein $_3$ subunit (SEQ ID NO: 1); (ii) methods for evaluating an individual's cardiac output in response to the beta- adrenergic receptor blocker propanolol by assaying for the presence of the 825 T allele of the gene encoding the human G protein $_3$ subunit (SEQ ID NO: 1); and (iii) methods of evaluating the response to prostaglandin E1 in subjects being treated for erectile dysfunction by assaying for the presence of the 825 T allele of the gene encoding the human G protein $_3$ subunit (SEQ ID NO: 1), does not reasonably provide enablement for methods for evaluating responsiveness of an individual to any in vivo pharmaceutical by assaying for a thymine at position 825 or a thymine at position 1429 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are broadly drawn to methods for evaluating responsiveness of an individual to an in vivo therapy by assaying for the presence of a substitution of a cytosine for a thymine at position 825 or 1429 of the human G protein $_3$ subunit

(GNB3). In particular, the therapy is treatment with hormones, transmitters, neurotransmitters or pharmaceuticals which activate G protein heterotrimers which contain the G protein subunits Gbeta3 or which stimulate the G protein subunit GalphaS. The claims also include methods for evaluating responsiveness to treatment with beta-adrenoreceptor blockers, erythropoietin, immunosuppressive agents, and prostaglandin E1. In particular, the specification (for example, page 35 and figure 8) teaches that individuals treated with the alpha-2-adrenergic agonist BHT933 show an increased reduction in coronary blood flow if they are carriers of the 825T allele. The specification also teaches that individuals treated with propanolol, an agent that blocks beta-adrenergic receptors, show an intensified decrease in cardiac output if they are carriers of the 825T allele. Furthermore, the specification teaches that individuals with the 825T allele show 2 times the risk of not reacting to prostaglandin E1 in the treatment of erectile dysfunction. However, the specification is not enabling for the invention as it is broadly claimed because the teachings and guidance provided i the specification are not commensurate with the claims. Firstly, it is noted that the claims are broadly drawn to methods which evaluate responsiveness to treatment. The claims do not clarify what is intended to be included by the step of evaluating. Thereby, methods of evaluating a response to therapy are considered to include, for example, methods which evaluate an increase response to therapy, methods which evaluate a decreased response to therapy and methods which evaluate any type of adverse response to therapy. The claims also include evaluating treating with any type of pharmaceutical agent used to treat any condition. However, the data provided in the specification is limited to methods

which use very specific agents to treat specific conditions. The results obtained with these agents and in these diseases cannot be extrapolated to all pharmaceutical agents and conditions. The fact that guanine nucleotide binding proteins (G proteins) have been found to be associated with specific disorders does not mean that the 825T allele of GNB3 is associated with all disorders. This finding further extends to the fact that while the 825T allele may be associated with some drug responses, the findings obtained with one drug response cannot be extrapolated to all other drug responses or to the response of these drugs in the treatment of other types of disorders. The art corroborates the unpredictability in the art of evaluating an individual's response to therapy by detecting the C825T mutation. For example, Serretti teaches that G proteins have been correlated with the pathophysiology and treatment of mood disorders and schizophrenia. However, Serretti reports that the 825 mutation is not associated with response to lithium in the treatment of mood disorders. Grossman teaches that the GNB3 is involved in the signal transduction pathway and vascular responses. Grossman found, however, that the GNB3 C825T polymorphism is not associated with vascular responses to acetylcholine (Ach). Secondly, while the 825T allele of GNB3 is thought to be associated with enhanced signal transduction via PTX-sensitive G proteins, the specific mechanism by which the 825T allele effects response to treatment remains unclear. For example, as stated by Naber (FEBS Letters (2000) 484: 199-201), "(f)uture studies will have to unravel the steps(s) which ultimately result in enhanced epinephrine-mediated aggregation in platelets from 825T carriers, which appears independent of inhibition of adenyl cyclase activity or platelet secretion."

Thirdly, the specification is not enabling for methods which detect the presence of the 1429 allele as indicative of response to in vivo therapeutics. The specification does not provide any data concerning the 1429 allele of GNB3 and response to any particular therapeutic. It is noted that the specification (page 8) states that the 1429 "polymorphism is in pronounced distribution equilibrium with the known C825T polymorphism." However, the specification has not clearly established that the linkage is sufficiently high so that the presence of the 1429T allele can be used to predict the response to therapy. That is, the specification has not established that the presence of the 1429T allele is always necessarily indicative of the presence of the 825T allele.

Lastly, the specification has not established that the Arg16Gly or Gln27Glu mutations in the beta-2 adrenergic receptor gene can be used to evaluate an individual's response to in vivo therapy. The specification does not provide any information regarding an association between these mutations and response to any type of therapy. There is no guidance provided in the specification as to how to determine, without undue experimentation, an association between these mutations and in vivo treatment with a therapeutic and as to how to determine how the presence of these mutations alters a response to therapy. Without specific guidance, the skilled artisan is left to randomly perform experiments in which populations are analyzed for the presence of these mutations, the populations are treated with a drug and all types of responses to that drug are monitored. Such experimentation is considered to be undue.

As stated in *Vaek* (20 USPQ2d 1438), the "specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed"

(emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art". With respect to the present invention, one cannot readily anticipate what additional treatments and response to treatments are associated with the 825T allele of GNB3. One cannot readily anticipate how the results obtained with the response to one therapeutic will extend to another therapeutic or to the treatment of another disease or to other responses to the therapeutic. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

RESPONSE TO ARGUMENTS:

In the response filed September 25, 2003, Applicants state that the specification at pages 11-35, "discusses the detail of the application of the present invention in prediction of diabetes mellitus (type II), adiposity/obesity, coronary heart disease and atherosclerosis, increased cholesterol, increased immune system function, increased t-lymphocyte, intensified progression of AIDS, osteoporosis, Alzheimer's Disease, erectile

dysfunction, thyroid gland dysfunction, increased pregnancy risks and low birth rate." However, while the specification does list each of these diseases, the specification fails to provide any details as to how a response to any form of treatment to these diseases can be evaluated by detecting either the 825 or 1429 polymorphisms. For instance, with respect to type-II diabetes, the specification states that there is a risk for type II diabetes for carriers of the 825T allele. However, the specification does not provide any information as to how the presence of this allele effects an individual's response to treatment. There are no teachings in the specification as to whether the polymorphism increases or decreases an individual's response to any particular and there is no information as to whether the 825T polymorphism is associated with increased or decreased side-effects in response to therapy. The specification leaves this research project to the practioner. Yet, this is the basis of the invention. The invention is not drawn to a method to evaluate the risk of having type-II diabetes. But, rather the invention is drawn to a method for evaluating an individual's responsiveness to a pharmaceutical. As set forth in the rejection, it is highly unpredictable as to whether the 825 polymorphism will be associated with responsiveness to therapy. This unpredictability is supported by the teachings in the art which demonstrate that the 825 polymorphism was not in fact correlated with response to specific pharmaceuticals used to modulate mood disorders and vascular responses. Accordingly, to practice the invention, the skilled artisan would have to detect the 825T polymorphism in a particular disease population, treat this population with a pharmaceutical, determine the responsiveness of this population to the pharmaceutical and compare the study

population's response to that of a second population that also received the therapy but did not contain the polymorphism and then determine whether the presence of the 825T polymorphism was in fact correlated with increased or decreased therapeutic effectiveness or was associated with any particular side-effects. Such experimentation is considered to be undue. There is no specific guidance or teachings in the specification to enable the skilled artisan to predict which responses to specific therapies will be correlated with the presence of the 825 polymorphism. Furthermore, the response does not address the rejection as it applies to the detection of the 1429 GNB3 mutation or the Arg16Gly and Gln27Glu mutations.

4. Claims 18-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18-27 are indefinite and vague because it is unclear as to how the method steps recited in the claims accomplish the objective set forth in the preamble of the claim. For example, claim 18 is drawn to a method for evaluating the responsiveness of an individual to an in vivo pharmaceutical. However, the claims recite a single step of evaluating a genetic modification. The claims do not clarify what is intended to be encompassed by evaluating a genetic modification. For example, it is unclear as to whether this refers to detecting a genetic modification or analyzing a genetic modification for some other unstated attribute. Further, the claims do not clarify how the step of evaluating or detecting a genetic modification results in the evaluation of an individual's response to an in vivo pharmaceutical.

RESPONSE TO ARGUMENTS:

In the response filed September 25, 2003, Applicants state that the meaning of "evaluating a genetic modification" would be clear to the skilled artisan. However, for the reasons stated in the rejection above, the phrase is not clear and this phrase renders the claims indefinite because the claims do not set forth the steps for accomplishing this objective. The claims recite that the method is one for evaluating responsiveness of an individual to a pharmaceutical. Yet, the claims include only a general step of evaluating a genetic modification. Evaluating a genetic modification includes simply detecting a genetic modification. The step of detecting a genetic modification is not equivalent to evaluating responsiveness to a pharmaceutical. The claims fail to provide the essential information and active process steps in which evaluating a genetic modification leads one to an evaluation of an individual's responsiveness to a pharmaceutical.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 18 and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Naber et al.

It is noted that Applicants have been given the filing date of March 12, 2001 because Applicants have not provided certified copies of the priority documents, nor certified translations of the non-English priority documents.

Naber teaches methods for evaluating the responsiveness of an individual to in vivo therapy with epinephrine wherein the method comprises detecting the presence of a C or T allele at position 825 of the GNB3 gene. The reference teaches that epinephrine activates PTX-sensitive G proteins and that alpha-2 adrenoreceptor activates G protein heterotrimers containing G 3 (page 199). Naber found that platelet aggregation was significantly enhanced following epinephrine treatment in 825T allele carriers and that this effect was more pronounced after inhibition of the cyclooxygenase-2 pathway by acetylsalicylic acid (page 200).

RESPONSE TO ARGUMENTS:

In the response filed September 25, 2003, Applicants request that the rejection be held in abeyance until the certified copies of the priority documents and certified translations are provided. However, it is not the Office's policy to hold rejections in abeyance. Accordingly, the rejections are maintained for the reasons of record.

6. Claims 18 and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Zill et al (NeuroReport (June 2000) 11: 1893-1897).

Zill (page 1894) teaches methods for evaluating the responsiveness of an individual to in vivo therapy with anti-depressants wherein the method comprises detecting the presence of a C or T allele at position 825 of the GNB3 gene. Zill reports

that there is an association between the TT genotype and better clinical response to anti-depressant treatment (see page 1896).

RESPONSE TO ARGUMENTS:

In the response filed September 25, 2003, Applicants request that the rejection be held in abeyance until the certified copies of the priority documents and certified translations are provided. However, it is not the Office's policy to hold rejections in abeyance. Accordingly, the rejections are maintained for the reasons of record.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. This phone number will be changed after January 13 to (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
December 17, 2003

CARLA J. MYERS
PRIMARY EXAMINER